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REVIEW ARTICLE

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Loperamide cardiotoxicity: "A Brief Review"

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Loperamide is a popular antidiarrheal medication that has been used for many years. It is currently gaining more attention among healthcare professionals due to its increasing potential for side effects. At present, it is considered safe enough to be sold over the counter. In contrast with other opioid agonists, loperamide is a peripherally acting μ-receptor agonist exerting its effects mainly on the myenteric plexus of the gastrointestinal longitudinal muscle layer. It decreases peristalsis and fluid secretion resulting in longer gastrointestinal transit time. The bioavailability of the drug is extremely low. Moreover, it is actively excluded from the central nervous system; hence, it lacks the central effects of euphoria and analgesia at the recommended dosages. Loperamide abuse has been steadily increasing in the United States. Abusers typically ingest high doses in desire to achieve a satisfactory central nervous system drug penetration. This has made it a potential over the counter substitute for self-treating opioid withdrawal symptoms and achieving euphoric effects.

KEYWORDS
Electrophsiology-long QT syndrome, Clinical electrophysiology-ventricular tachycardia, Clinical electrophysiology-cardiac arrest/sudden death, Clinical ion channels and membrane transporters

1 | INTRODUCTION

Opioid use is a major public health dilemma and a growing epidemic across the United States (Marraffa et al., 2014). Loperamide is a peripheral μ-opiate agonist exerting antisecretary and antimotility activity in the intestines via its effect on the myenteric plexus of the longitudinal muscle layer (Ooms, Degryse, & Janssen, 1983; Regnard, Twycross, Mihalyo, & Wilcock, 2011) Moreover, there might be a role for calcium channel antagonism in at least part of its antidiarrheal effects (Reynolds, Gould, & Snyder, 1984). Loperamide has been used successfully for many years in patients with chronic diarrhea (Regnard et al., 2011). Its lack of central nervous system (CNS) activity due to nominal penetration of the blood–brain barrier (BBB) has made it a popular first-line choice for chronic diarrhea (Regnard et al., 2011).

2 | PHARMACOLOGY

Loperamide is a phenylpiperidine derivative with a chemical structure similar to diphenoxylate and haloperidol (Baker, 2006). It is considered nonabsorbable when ingested orally, with a bioavailability of <2%; thus, only minimal amounts reach the systemic circulation (Lääveri, Sterne, Rombo, & Kantele, 2016; Regnard et al., 2011). Moreover, even if increased plasma concentrations were achieved, the drug is a substrate for the ATP–dependent efflux membrane transporter P-glycoprotein, which actively excludes it from the CNS (Sadeque, Wandel, He, Shah, & Wood, 2000). It is completely metabolized by cytochrome P450 (mainly CYP3A4) in the liver where it is conjugated and excreted with bile acids (Regnard et al., 2011). The half-life of loperamide is about 11 hr, and it's time to peak concentration is about 2.5–5 hr (Marraffa et al., 2014; Regnard et al., 2011). Nevertheless, half-lives of up to 40.9 hr have been reported with the maximum recommended dose of 16 mg in healthy volunteers (Eggleston, Nacca, & Marraffa, 2015; Yu et al., 2004).

3 | POTENTIAL FOR ABUSE

Loperamide was first produced by Paul Janssen of Janssen Pharmaceutica in 1969. It was initially approved for use by FDA on

December 28, 1976 (Stanciu & Gnanasegaram, 2016). Nowadays, it is widely available as a nonprescription medication since 1988 (Vakkalanka, Charlton, & Holstege, 2017). Also, it is on the World Health Organization's List of Essential Medicines (World Health Organization, 2015) Unfortunately, due to its easy obtainability and relatively inexpensive cost, unregulated use is common among the population, especially for controlling gastrointestinal symptoms, primarily diarrhea. Subsequently, this has led to an increase in its nonillicit drug use, and made it particularly favored among opioid users (Hurtado-Torres & Sandoval-Munro, 2016). Doses of 40–100 times the recommended antidiarrheal dose are typically reached. Moreover, with the growth of Internet and social media use, information describing techniques for using loperamide is becoming readily available and encouraged among people either for self-treatment of opioid withdrawal symptoms or for recreational use (Daniulaityte et al., 2013). Between 2010 and 2015, there was a 91% increase in intentional nonmedical use of loperamide (Vakkalanka et al., 2017). The maximum recommended dose of loperamide is 16 mg/day. At this dose, loperamide effects are limited to the gut (Vaughn, Solik, Bagga, & Padanilam, 2016). However, it appears that it might have CNS effects at higher doses. This can be attributed to the saturation of P-glycoprotein transporters; therefore, enabling loperamide to cross the BBB and activate central opioid receptors leading to euphoria and analgesia (Crowe & Wong, 2003). Inhibition of P-glycoprotein is well-known in the modulation of morphine-induced behavioral effects and tolerance by increasing opiate transport across the BBB (Seleman et al., 2014). Many agents are known to antagonize the P-glycoprotein system including loperamide itself, ketoconazole, cyclosporine, cimetidine, and quinidine (Ayrton & Morgan, 2001; Stanciu & Gnanasegaram, 2016; Tan-No et al., 2003). Furthermore, P-glycoprotein has been shown to be involved in the development of tolerance to loperamide within the GI tract (mainly in animal models) (Kolbow, Weitschies, & Siegmund, 2016; Tan-No et al., 2003). This is in contrast with other opioids such as morphine where gastrointestinal tolerance and more specifically colonic tolerance does not develop. Hence, this signifies the differences in signaling and receptor regulation (Akbarali, Inkisar, & Dewey, 2014; Kolbow et al., 2016; Tan-No et al., 2003).

4 | LOPERAMIDE CARDIOTOXICITY

The growing abuse of loperamide along with multiple case reports addressing cardiac side effects have instigated the FDA to issue a warning on June 7, 2016 about serious cardiac events resulting from abuse and misuse (Administration UFaD, 2016). Most of these cardiac events occurred in individuals intentionally using high doses of the drug for self-treatment of opioid withdrawal or to attain the desired feeling of euphoria. Recently, numerous reports of dramatic QT prolongation, wide complex tachycardias, polymorphic ventricular tachycardias and sudden cardiac death associated with loperamide abuse have been described (Enakpene, Riaz, Shirazi, Raz, & Indik, 2015; Marraffa et al., 2014; Spinner, Lonardo, Mulamalla, & Stehlik, 2015; Vaughn et al., 2016).

The mechanisms underlying proarrhythmic effects of loperamide are most likely related to the inhibition of the sodium/potassium (Na^+/K^+) transmembrane ion channels in the cardiac cells. The resultant QRS prolongation is most likely related to delays in depolarization while QT prolongation usually reflects delays in repolarization.

Whereby, the *human ether-a-go-go-related* gene (hERG) channel is likely involved in loperamide-induced fatal cardiac arrhythmias. The hERG channel forms a major portion of the ion channel proteins which conducts potassium ions (K^+) out of the myocardial cells, and is crucial in appropriately repolarizing the cell membrane during the cardiac action potential (Sanguinetti & Tristani-Firouzi, 2006). In the ventricles, loss of function mutations in genes encoding potassium channels (mainly hERG channels) are related to hereditary long QT syndrome putting these patients at risk for sudden cardiac death (SCD). Mutations in the genes for KvLQT1 (I_{Ks}) and hERG (I_{Kr}) account for 80%–90% of all hereditary long QT syndrome (Ravens & Cerbai, 2008). Moreover, the hERG channel is also susceptible to low extracellular potassium levels as well as drug binding, both of which can cause decreased channel function and acquired or drug-induced long QT syndrome. Thereby, placing individuals at risk for developing polymorphic ventricular tachycardia and ventricular fibrillation leading to SCD (Ravens & Cerbai, 2008; Sanguinetti & Tristani-Firouzi, 2006; Taira, Opezzo, Mayer, & Hocht, 2010).

In one experiment, simulated loperamide testing was done on the most abundant cardiac sodium channel ($Na_v1.5$) and the two main repolarizing potassium channels: K_vLQT1/minK and the hERG channel (Kang, Compton, Vaz, & Rampe, 2016). It was found that loperamide can inhibit all three channels with different affinities; specifically it had a very high inhibitory action on the hERG channel (Kang et al., 2016). In another study, similar results were demonstrated; whereby, loperamide was shown to exhibit a concentration-dependent blockade of hERG current with significant prolongation in the action potential duration (Klein et al., 2016). These effects are thought to be responsible for the electrocardiogram (ECG) changes of QRS and QT prolongation as the inhibitory action can affect both depolarization and repolarization.

Moreover, there have been recent case reports about loperamide-induced Takotsubo cardiomyopathy (TTC) while the mechanism behind this observation remains unclear (Bhatti, Norsworthy, & Szombathy, 2017; Patel, Shah, & Subedi, 2017). In TTC, the most commonly agreed upon mechanism is catecholamine-mediated myocardial dysfunction secondary to sympathetic nervous system overactivation. Thus, it can be hypothesized that these reported patients had TTC either secondary to the stress of hospitalization, or possibly loperamide-withdrawal leading to catecholamine release, or even through direct effects of loperamide on the myocardial cells.

With regard to treatment of loperamide-induced cardiotoxicity, various agents have been tried including atropine, amiodarone, lidocaine, metoprolol, magnesium, and sodium bicarbonate. Furthermore, the use of pharmacological and electrical pacing was necessary in some cases to achieve heart rate overdrive for arrhythmia control. (Marraffa et al., 2014; Marzec et al., 2015; Mukarram, Hindi, Catalasan, & Ward, 2016; O'Connell et al., 2016; Spinner et al., 2015; Upadhyay et al., 2016; Wightman et al., 2016).

5 | CONCLUSION

In conclusion, loperamide abuse is projected to increase in the absence of any regulatory measures. Healthcare providers should consider loperamide misuse when managing patients with opioidlike toxicity, especially in the setting of QRS interval widening and QT prolongation. In addition, increased control over the availability of nonprescription loperamide should be warranted.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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